REMARKS

In response to the Restriction Requirement, Applicants hereby provisionally elect, with traverse, the invention of Group I, claims 1-30, this group being drawn to methods of dissociating protein chains of Arenicola marina, methods of preparing primers and thereby DNA set forth as SEQ ID NO:1, and said DNA expression product.

The grounds for traversal are as follows.

The instant application is a 371 National stage application of PCT/FR2004/002602, and thus, PCT rules apply.

PCT Rule 13.1 requires that an international application relate to one invention only or to a group of inventions so linked as to form a single general inventive concept (unity of invention). PCT Rule 13.2 provides that unity of invention is fulfilled when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The phrase "special technical features" means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. When the Office considers international applications during the national stage, PCT Rule 13.1 and 13.2 must be followed when considering unity of invention without regard to practice in national applications filed under 35 U.S.C. §111. PCT Rule 13.3 further states that the determination whether a group of inventions is so linked as to

form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

The inventions of Groups I - X share a technical relationship involving one or more special technical features that define over the prior art. The DNA set forth as SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 encode protein chains that are structurally and functionally related. Thus, one or all of Groups II - X should be examined together with Group I.

The present invention is directed to the extracellular hemoglobin molecules of *Arenicola marina* (marine lugworm). The hemoglobin molecule is made up of multiple polypeptides broadly divided into two categories: the "functional" polypeptides carrying the active site capable of reversibly binding oxygen, and the "structural" (or "linker") polypeptides allowing the proper assembly of the hemoglobin molecule. The functional polypeptides are the globin-type peptides similar to the α and β-type chains of vertebrate hemoglobin (*see,* page 5 of the specification).

By way of illustration, in adult humans, the most common hemoglobin type is a tetramer (which contains 4 subunit proteins) called hemoglobin A, consisting of two α and two β subunits non-covalently bound, each made of 141 and 146 amino acid residues, respectively. This is denoted as α2β2. The subunits are structurally similar and about the same size. Each

subunit has a molecular weight of about 17,000 daltons.

Several hemoglobin variants exist. For example, variants in humans exist as a part of the normal embryonic and fetal development. Mutant forms of hemoglobin also exist as a result of genetic variations. Some well-known hemoglobin variants such as sickle-cell anemia are responsible for diseases; other variants cause no detectable pathology, and are thus considered non-pathological variants.

In the embryo: Gower 1 ($\zeta 2\varepsilon 2$), Gower 2 ($\alpha 2\varepsilon 2$), Hemoglobin Portland ($\zeta 2\gamma 2$).

In the fetus: Hemoglobin F ($\alpha 2\gamma 2$).

In adults: Hemoglobin A ($\alpha 2\beta 2$), Hemoglobin A2 ($\alpha 2\delta 2$), Hemoglobin F ($\alpha 2\gamma 2$).

Variant forms which cause disease: Hemoglobin H ($\beta 4$), Hemoglobin S ($\alpha 2\beta S2$), Hemoglobin C ($\alpha 2\beta C2$).

Although hemoglobin variants exist, each of the subunits continues to share structural and functional similarity with the other subunits. The various subunits, e.g. α, β, or γ-type, and the variants within each subunit, e.g., $\beta 2$, $\beta S2$, $\beta C2$, maintain structural and functional similarity.

The present application includes claims directed to methods for obtaining proteins constituting the *Arenicola* hemoglobin molecule, primer pairs to amplify nucleic acid coding for the proteins, the proteins encoded by the nucleic acid, and the nucleic acid encoding the proteins. The claimed proteins

and nucleic acids, set forth by SEQ ID NOs: 1-20, are all directed to subunits of the hemoglobin molecule. The subunits share structure and function. For example, SEQ ID NO: 1 encodes the globin A2a gene (SEQ ID NO: 2). SEQ ID NO: 3 encodes for the globin A2b gene (SEQ ID NO: 4). As detailed above, the two globin subunits comprise structural variants of hemoglobin. Evidence of the structural similarity is shown by the use of identical antisense primers (SEQ ID NO: 20) to amplify the DNA (*see*, page 42 of the specification).

In fact, SEQ ID NOs: 5, 7, 9 and 11 encode for the globin A1, B2, B1 and L1 genes (SEQ ID NO: 6, 8, 10 and 12) respectively, and each is also a structural variant of hemoglobin. Again, the use of the identical antisense primer (SEQ ID NO: 20) to amplify each gene proves that structural similarity exists (*see*, pages 43-44 of the specification).

For the same reasons, the nucleic acids and proteins of SEQ ID NOs: 13 - 19 share structural similarity, the difference here being the use of an optional step of 5' RACE PCR to extend the nucleic acid sequence.

In contrast to the position stated in the Office Action, at page 3, the inventions listed as Groups I-X do relate to a single inventive concept under PCT Rule 13.1. The nucleic acids encoding the different protein chains of *Arenicola marina* hemoglobin share the same structure and function, and therefore, have the same or corresponding special technical features.

The MPEP guidance for determining unity of Markush grouping of alternatives of chemical compounds provides that the compounds are of a similar nature where: (A) all alternatives have a common property or activity; and (B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives; or (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds (*see*, MPEP, 1850). In this case, the inventions of Groups I-X clearly satisfy these criteria. The hemoglobin subunits and their variants have a common property and activity, have a common structure, share a significant structural element, and belong to a recognized class of compounds.

As further set forth in the MPEP, "[a]lthough lack of unity of invention should certainly be raised in clear cases, it should neither be raised nor maintained on the basis of a narrow, literal or academic approach. There should be a broad, practical consideration of the degree of interdependence of the alternatives presented, in relation to the state of the art as revealed by the international search or, in accordance with PCT Article 33(6), by any additional document considered to be relevant. . . . [If] there is a single general inventive concept that appears novel and involves inventive step, then there is unity of invention and an objection of lack of unity does not arise." (*see*, MPEP, 1850).

An international application must relate to one invention or to a group of inventions so linked as to form a single general inventive concept. Observance of this requirement is checked by the International Searching Authority. As stated in the MPEP, "it is clear that the decision with respect to unity of invention rests with the International Searching Authority." (*see*, MPEP, 1850). The present application was examined by the European Patent Office as International Searching Authority. As acknowledged by the International Search Report of the present application (PCT/FR2004/002602), the International Searching Authority appears to have maintained that unity of invention exists for all of the claims. The International Search Report failed to indicate a lack of unity. The Office is required to follow the same standard for unity of invention as currently established.

The Examples provided in Chapter 10 of the International Search and Preliminary Examination Guidelines further illustrate that unity of invention exists between the claims of Groups I-X. In Example 33: Multiple Structurally and Functionally Related Polynucleotides, the claimed polynucleotides all share a significant structural element and their corresponding mRNAs are expressed only in a specific cell type (hepatocytes). The polynucleotides would be regarded as having the same or corresponding technical feature if the alternatives had a common property or activity, and shared a significant

structural element that is essential to the common property or activity. In the instant application, as detailed in the remarks above, the claimed polynucleotides all share significant structural elements, i.e., hemoglobin subunit variants, that is essential to the common property or activity, i.e., oxygen binding, stabilization, and release. The corresponding genes are expressed only in *Arenicola*, specifically the extracellular hemoglobin. Since both of these requirements are met, the group of polynucleotide molecules claimed meets the requirement of unity of invention.

A second example, Example 36: Multiple Nucleic Acid Molecules Which Share Common Structure and Encode Proteins with Common Property, is also illustrative of how unity of invention can be determined in this application. This example has three nucleic acids encoding dehydrogenases that include a conserved sequence motif defining the catalytic site and dehydrogenase function of these proteins. The three nucleic acids (SEQ ID NOs: 1-3) share significant sequence homology (85-90%) at both the nucleotide and amino acid sequence levels. This example also factors in some cited prior art, and exemplifies how the technical feature shared between the inventions must define a contribution over the prior art. In this application, the Office Action fails to cite any relevant prior art that could be used to show that the same or corresponding technical feature shared among the nucleic acid molecules does not define over the prior

art. Thus, according to this example, the technical feature would be special and SEQ ID NOs 1-3 would have unity of invention.

Similarly, Example 37: DNA Encoding Receptors with Partial Structural Identity and Asserted Common Property provides very useful guidance to prove unity of invention in the instant application.

For all of the reasons set forth in the remarks above, Applicants respectfully traverse the Examiner's objection for absence of a common technical feature among Groups I-X. Applicants submit that the Official Action fails to satisfy the requirements of PCT Rule § 13.1 and PCT Rule § 13.2. Applicants submit that the present claimed invention is a contribution over the prior art and that unity of invention for Groups I-X should be recognized.

Therefore, Applicants believe that all of the claims are sufficiently related so as to warrant a search and examination of all the claims in their full scope. Favorable action on the merits is solicited.

Should there be any matters that need to be resolved in the present application, the Examiner is requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any

overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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